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Ertapenem in outpatient parenteral antimicrobial therapy for complicated urinary tract infections

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Ertapenem in outpatient parenteral antimicrobial therapy for complicated urinary tract infections

Abstract

Background: Ertapenem is a broad-spectrum antibiotic that is increasingly being utilized. Its dosing convenience renders it suitable for outpatient therapy, and its pharmacokinetic characteristics favour its use against complicated urinary tract infections (cUTIs). Despite this, sufficient clinical data are lacking for its use against cUTIs in the outpatient setting. We assessed the microbiological and clinical cure rates associated with ertapenem treatment for cUTIs in two outpatient parenteral antimicrobial therapy (OPAT) departments. **Methods:** We undertook a prospective observational study of adult patients who received ertapenem for cUTIs between August 2010 and August 2014. Data on patient characteristics, clinical progress and microbiological results were collected and analysed. **Results:** Sixty-one patients were enrolled. The median age was 59 years (range 24, 83) and 61% were male. The most common diagnoses were pyelonephritis (39%) and prostatitis (15%). The most common causative organism was *Escherichia coli* (67%). Extended-spectrum β -lactamase (ESBL)-producing organisms were detected in 72% of infections. Microbiological cure was achieved in 67% overall, and was less likely in those with *Klebsiella pneumoniae* infection (OR = 0.21 [95%CI: 0.05 to 0.85] $p = 0.029$). Clinical cure was observed in 92% of patients. **Conclusion:** In this study of treating cUTIs with ertapenem, we have demonstrated good clinical outcomes. A lower than expected microbiological cure rate was observed in those with *Klebsiella pneumoniae* infection.

Keywords

therapy, complicated, urinary, antimicrobial, infections, parenteral, tract, outpatient, ertapenem

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20 **KEYWORDS:** Complicated Urinary Tract Infections; Outpatient Parenteral Antimicrobial Therapy; Ertapenem;
21 Multi-Drug Resistant Organisms.

1. Introduction:

Complicated urinary tract infections (cUTIs) occur in those with a functionally, metabolically, or anatomically abnormal urinary tract, in addition to catheterised patients[1]. The clinical spectrum ranges from mild cystitis to life-threatening sepsis. Management of UTIs includes the use of a variety of broad-spectrum antimicrobials[2]. Recently, emerging resistance mechanisms have rendered common antimicrobial agents less effective. Current practice recommends 10 to 14 days of therapy with an antimicrobial agent active against a wide range of gram-negative bacilli[2]. With the changing epidemiology of extended-spectrum β -lactamase (ESBL) producing organisms, the antibiotic options will be increasingly limited, rendering carbapenems as the treatment of choice for serious infections due to ESBL-producing organisms[3].

Ertapenem has excellent antimicrobial activity against a broad spectrum of pathogens associated with hospital and community-acquired infections, including ESBL producing gram negative organisms, which are commonly implicated in UTIs[4]. It has narrower activity compared with other carbapenems, and has a low minimum inhibitory concentration (MIC) against ESBL producing organisms rendering it an effective first line agent[5]. Furthermore, its excretion in the urine gives it a favourable pharmacokinetic profile to treat cUTIs[6]. In a well-designed study, ertapenem was found to be as efficacious as ceftriaxone in treating a cohort of cUTIs with non-ESBL producing gram negatives[7].

In the outpatient setting, there are few studies on cohorts of patients with cUTIs caused by ESBL producing gram-negative organisms[8-10]. Given that ertapenem can be administered once daily it is suitable for use in outpatient therapy. Treating infections in the outpatient setting has been proven cost effective and safe[11]. Hence, we conducted this study to establish the efficacy of ertapenem in treating cUTIs in the outpatient setting.

2. Methods:

We undertook a prospective, open-label, observational study through two of Singapore's largest outpatient parenteral antimicrobial therapy (OPAT) centres over a 4-year period. Eligible patients were those that were prescribed intravenous (IV) ertapenem 1g, or a renally adjusted dose, every 24 hours as outpatients (either initially as inpatients or for the full duration). Our study was approved by the Institutional Review Board covering both hospitals.

Inclusion criteria included non-pregnant adult patients greater than 21 years of age with cUTI as defined by Rubin et al, [12] due to a pathogen susceptible to ertapenem isolated in urine or blood, and those with favourable clinical response to initial therapy in hospital, where applicable. Patients with hypersensitivity reactions to ertapenem or in whom an informed consent could not be obtained were excluded.

As an observational study the investigators had no input into the duration of treatment. Patients were monitored daily at the OPAT centre. This included clinical assessment for improvement of presenting complaints and potential adverse events. Serum creatinine, electrolytes and white blood cell count, and urinalysis were performed routinely or when clinically indicated. Mid-stream urine cultures were performed on the last day of therapy (± 3 days). After completion of treatment, patients were assessed by an infectious diseases physician at 30 days (± 7 days) with repeat urinalysis and mid-stream urine culture.

The primary outcome of the study was microbiological cure, which was defined as a negative culture on any occasion after treatment. Those with the same organism isolated any time following therapy were considered as persistent infection, and those who developed a new microorganism were considered as having a superinfection, regardless of whether they developed symptoms. The secondary outcome of the study was clinical cure defined as complete resolution of symptoms and signs at diagnosis. Outcome was assessed as therapy success or failure. Failure was defined as developing adverse outcomes in addition to change of therapy, hospital re-admission due to cUTI and mortality.

Bacteria were identified by matrix associated laser desorption ionization time of flight mass spectrometry (MALDI-TOF-MS, Bruker Daltoniks GmHB, Bremen, Germany). Antibiotic susceptibility was determined using VITEK II (bioMerieux S.A., Marcy l'Etoile, France), and interpreted using breakpoints according to EUCAST..

For descriptive analysis, the means and their standard deviation (SD), or medians with their range were reported. Chi-square or Fisher's exact tests were used to compare categorical variables; *t*-test and Mann–Whitney tests to compare continuous variables. A multivariate logistic regression model with variables in univariate analysis at a $P < 0.2$ level was constructed. Using backward selection, variables were retained in the final logistic regression model if their significance remained below $P = 0.2$. All tests were conducted at the 5% level of significance, with odds ratios (OR) and corresponding 95% confidence intervals (CI) reported. All statistical analyses were performed using Stata 9.0 (Stata Corp., College Station, TX, 2005).

3. Results and data analysis:

A total of 61 patients were studied. Baseline demographic features and disease characteristics are summarised in Table 1. Of the patients 61% were male, and ethnic diversity represented that of Singapore with 62% being of Chinese ethnicity. Of all patients 24 (39.3%) had pyelonephritis and 11 (18%) had prostatitis. Six (9.8%) had associated bacteraemia and were classified as urosepsis, and 20 (32.8%) had a diagnosis of cystitis. The duration of treatment in the outpatient setting was of a mean of 10 days (SD= ± 7.5). The total duration of therapy including inpatient and outpatient therapy was of a mean of 22 days (SD= ± 11.8).

Frequently isolated pathogens were *Escherichia coli* and *Klebsiella pneumoniae*, recovered from 41 (67.2%) and 14 (23%) respectively. Other cases demonstrated both *E.coli* and *K. pneumoniae* (3 patients), *Morganella morganii* (2 patients) and 1 had negative cultures (clinical diagnosis as pyelonephritis). All isolates were susceptible to ertapenem. Out of 60 isolates, 41 (68%) were ESBL producers. Twenty-seven (66%) of the *E.coli* isolates and 12 (86%) of the *K. pneumoniae* isolates were ESBL-positive (Table 2).

Five patients discontinued therapy early, one due to clinical treatment failure, another for persistent symptoms with additional therapy added and 3 due to adverse reactions. All those completing treatment had a follow up culture undertaken a median time of 30 days (range: 4-40) after cessation of ertapenem. Forty-one (68%) had microbiological eradication, 9 (15%) had persistence of the infecting bacteria, and 11 (18%) had a different organism isolated. Nine out of those 11 had total resolution of symptoms (Table 3). Clinical cure was obtained in 56 (92%) having complete resolution of signs and symptoms. Only 1 (2%) had no improvement in symptoms and had additional therapy. Three (5%) developed adverse drug reactions attributable to ertapenem. One stopped treatment on day 5 of therapy due to rash, but had microbiological eradication and resolution of signs and symptoms. Two others developed headache and vomiting, and were switched to alternative therapy.

There were 40 (65%) patients who achieved both clinical cure and microbiological eradication, while 9 (15%) had a clinical cure with a different organism cultured, and 7 (11%) had the same organism isolated but with clinical cure achieved. Only 2 (3%) were classified as microbiological persistence with clinical failure.

Multivariate logistic regression showed that having an infection with *K. pneumoniae* at baseline was found to be a risk factor for not achieving microbiological cure (OR=0.21 [95%CI: 0.05 to 0.85] p=0.029). Compared with other ethnicities, Indians were more likely to achieve microbiological failure (OR=4.47 [95%CI: 1.06 to 18.9] p= 0.042). There were no risk factors identified for not achieving clinical cure on univariate analysis, and hence a multivariate analysis was not conducted.

The mean duration of therapy for those who achieved microbiological cure was 23.6 days (SD=+/- 12.9), and for those who did not was 17.9 days (SD= +/- 8.4), but the difference was not significant (p=0.08). Similarly, those achieving clinical cure had a mean duration of therapy of 22.4 days (SD= +/- 12.3), compared with 16.9 days (SD=+/- 7.2) for those who had no clinical cure (p = 0.219). ESBL status had no impact on outcomes in our cohort (microbiological cure p=0.695, clinical cure p=0.663).

4. Discussion

In this study, the safety and efficacy of ertapenem in the OPAT setting were demonstrated for the treatment of cUTIs. The overall clinical success rate among patients was 92%, while 3 (5%) patients discontinued therapy due

to adverse effects. A total of 52 (85%) had their original organisms eradicated (Table 3). None of the non-ESBL organisms developed resistance following ertapenem therapy. Patients who had *K. pneumoniae* infection prior to commencing therapy were less likely to achieve microbiological eradication. Indeed, the microbiological cure rate in those with *K. pneumoniae* was (50%), and significantly contributed to the overall microbiological cure rate (67%). Of those without microbiological eradication none were re-admitted in the subsequent 3 months for cUTI.

Our study was limited by its observational nature and the relatively small number of participants making subgroup analysis difficult. Furthermore, it was a single-arm study with no comparator. The study did not look at outcomes of cUTIs treated by other antimicrobials. Being an OPAT study, there was clearly a selection bias towards patients who were well enough to continue therapy as outpatients, but the safety and efficacy of ertapenem has been previously established in the inpatient setting [5, 13-15]. By following well-established microbiological definitions [12], the study's primary outcome was microbiological eradication, which may not reflect real life clinical contexts, where a positive microbiology could indicate colonization rather than infection. This may have reflected on the relatively prolonged mean duration of therapy, which was not associated with outcome, suggesting that longer courses were not necessary.

The largest OPAT cohort prior to our study included 50 patients, but it was in a paediatric population[16]. Similarly, studies conducted in outpatient populations who received ertapenem included even smaller numbers[8-10], with one study including women with simple cystitis. This study demonstrated that ertapenem is a good alternative to broader-spectrum carbapenems in the treatment of cUTIs. As well as being safe and effective it has the advantages of a narrower spectrum and lends itself to an OPAT setting being a once daily dosing.

Declarations:

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Competing interests: None declared

Ethical approval: This study was approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB)

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Table 1: Baseline characteristics of patients with cUTIs, (n=61) and their univariate analysis against microbiological cure rates following therapy with ertapenem						
Characteristics	Frequency (n=61) (%)	Microbiological cure (%)	Microbiological failure (%)	Odds Ratio	95% CI	p- value
Male (n [%])	37 (60.7)	70.2	29.7	1.15	0.73-1.83	0.584
Chinese (n [%])	38 (62.3)	68.4	31.6	1.17	0.39-3.46	1.0
Indian (n [%])	11 (18.0)	45.5	54.5	0.32	0.09-1.23	0.153*
Malay (n [%])	7 (11.5)	71.4	28.6	1.25	0.22-7.08	1.0
Other ethnicity (n [%])	5 (8.2)	100	0	0.88	0.78-0.98	0.162
Mean age (+/- SD)	59 (+/-16)	59 (+/-15)	61 (+/-17)	N/A	N/A	N/A
>65 years (n [%])	35 (57.4)	88.6	11.4	1.17	0.56-2.42	0.651
<i>K. pneumoniae</i> on intitial culture (n[%])	14 (22.9)	43	57	0.26	0.07-0.89	0.049*
ESBL detected	41 (67)	75.6	24.4	1.26	0.40-3.93	0.772
Pyelonephritis (n [%])	24 (39.3)	75	25	1.83	0.58-5.7	0.405
Prostatitis (n [%])	11 (18)	64	36	0.82	0.21-3.22	0.78
Urosepsis (n [%])	6 (9.8)	83.3	16.7	2.64	0.29-24.2	0.351

Cystitis (n [%])	20 (32.8)	55	45	0.45	0.15-1.37	0.245
No. of days on therapy in OPAT (mean +/- SD)	10 (+/-7.5)	10.5 (+/-7.4)	10.3 (+/-7.9)	N/A	N/A	0.835
No. of days on therapy (inpatient & OPAT) (mean+/-SD)	22 (+/- 11.8)	23.6 (+/-12.9)	17.9 (+/-8.4)	N/A	N/A	0.08
* entered into multivariate model						

Table 2: Microbiological characteristics and outcomes of patients with complicated urinary tract infections (n=61). Note: Patients with mixed *E.coli* and *K. pneumoniae* (n=3), *M. morganii* (n=2), and no significant growth (n=1) are not included.

	<i>ESBL detected (%)</i>	<i>ESBL not detected (%)</i>	<i>Total (%)</i>
<i>E. coli</i>	27	14	41
<i>Clinical Cure</i>	24 (89)	13 (93)	37 (90)
<i>Microbiological Cure</i>	21 (78)	10 (71)	31 (76)
<i>K. pneumoniae</i>	12	2	14
<i>Clinical Cure</i>	10 (83)	2 (100)	12 (86)
<i>Microbiological Cure</i>	6 (50)	0 (0)	6 (43)

Table 3: Clinical and microbiological outcomes (n=61)			
	Clinical Cure	Clinical Failure	Total
Microbiological cure	40 (65%)	1 (2%)	41 (67%)
Microbiological superinfection*	9 (15%)	2 (3%)	11 (18%)
Microbiological persistence	7 (11%)	2 (3%)	9 (15%)
Total	56 (92%)	5 (8%)	61**
<i>*Those who had a new micro-organism isolated at the end of therapy or on follow-up, **Including one patient with pyelonephritis (no isolated micro-organism at diagnosis) but who had clinical cure and clear urine culture following empiric treatment with ertapenem.</i>			